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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,761	09/22/2004	Gerard Martin Paul Giblin	P33027USW	8296

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/508,761	GIBLIN ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-12 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25* is/are allowed.

6)☒ Claim(s) *1-5,7,10-12 and 17-24* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/22/04;4/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claim 6 is objected to because of the following informalities: The phrase "3-" is missing in front of the first compound named "{2-[5-chloro-2-(benzyloxy)-phenyl]-cyclopent-1-entyl}-benzoic acid" in line 2 of the claim, on page 5 of the claims.. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 10-12, 17-18, 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula (I) wherein A is phenyl or a 6 membered heteroaryl ring with 2 N, or a 5 membered heterocyclic ring with 1 to N, or a morpholine ring and Rx equal to optionally substituted cyclohexylmethylene or benzyl, and R2 equal to halo, halogenated alkyl, or alkyl, does not reasonably provide enablement for using the compounds wherein A is all other heterocyclic rings claimed, R2 is all other substituents claimed, and Rx is equal to all other substituents claimed. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

a) Determining if any particular claimed compounds of formula (I) wherein A is any of the substituents claimed other than phenyl or a 6 membered heteroaryl ring with 2 N, or a 5 membered heterocyclic ring with 1 to N, or a morpholine ring and Rx are any of the substituents claimed other than optionally substituted cyclohexylmethylene or benzyl rings, and R2 are any of the substituents claimed other than halo, halogenated alkyl or alkyl would be active, would

require synthesis of the substrate and subjecting it to testing with Applicants' functional calcium mobilization assays. Considering the large number of compounds to be made, this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found on pages 35-164, which merely states Applicants' intent to make and use such compounds. c) In the instant case, none of the working examples contains any radical A equal to substituents claimed other than phenyl or a 6 membered heteroaryl ring with 2 N, or a 5 membered heterocyclic ring with 1 to N, or a morpholine ring; Rx equal to any of the other substituents claimed other than optionally substituted cyclohexylmethylene or benzyl rings; R2 equal to any other substituent claimed other than halo, halogenated alkyl or alkyl.

d) The nature of the invention is a method of treating a human or animal subject suffering from a condition mediated by the action of PGE2 at EP1, or from pain associated with migraine, inflammatory pain, neuropathic pain, or visceral pain, or from inflammatory, immunological, bone, neurodegenerative or renal disorder with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the EP1 and EP3 receptor, the binding activity of small ligands to these receptors, and the ability of those compounds to selectively antagonize the EP1 receptor over the EP3 receptor. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) For example, the six-membered benzene ring of Applicants' working in the Rx moiety in the examples, such as example 3, is non-basic. The pyridine ring, pyrimidine ring, and the pyrazine ring of the rejected compounds are strongly basic, basic, and weakly basic

respectively. The pyridine ring and the pyrazine ring of the rejected compounds are hydrogen bond acceptors. The benzene ring of Applicants' working examples is not. The pyridine ring and the pyrazine ring of the rejected compounds are π-electron deficient. The benzene ring of Applicants' working examples is not. There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (I) will all share the same biological properties. The diverse claimed heteroaryl rings and heterocyclyl rings and non-ring structures, are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In

view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 21, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating some inflammatory, neuropathic or visceral pain, and some immunological, bone, neurodegenerative or renal disorders, does not reasonably provide enablement for treating all types of pain, or all types of immunological, bone,

neurodegerative or renal disorders or all conditions which are mediated by the action of PGE2 at EP1 receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 18, 21, 22, and 23 is the treatment of an any condition which is mediated by the action of PGE2 at EP1, any type of pain, or inflammatory, bone, neurodegenerative or renal disorders, or any type of inflammatory pain, neuropathic pain, or visceral pain with the claimed compounds.

The State of the Prior Art

The state of the art is that EP1 is a receptor for one of the prostaglandins (PGE2). See page 325 of Stock et. al. Knock out mice for the EP1 receptors have reduced nociceptive pain perception as well as altered cardiovascular homeostasis. Studies indicate that signaling through the EP1 receptor accounts for a major component of the effect of nonsteroidal anti-inflammatory drugs to ameliorate pain. Inhibition of the COX pathway using gene targeting or pharmacological inhibitors have demonstrated the importance o prostaglandins, and specifically PGE2, in mediating pain and/or inflammation. Page 330 of Stock et. al., Experimental findings

have shown that the analgesic actions of nonsteroidal drugs in inflammatory pain, especially visceral stimuli, are mediated to a significant degree by inhibition of signaling through the EP1 receptor. See page 331 of Stock et. al.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of EP1-mediated diseases, whether the EP1 was activated or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compound of the claims and the antagonizing of EP1, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of EP1 in all of all inflammatory disorders, all types of pain, or all types of immunological, bone, neurodegerative or renal disorders or all conditions which are mediated by the action of PGE2 at EP1 receptors. , i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of the claims can antagonize the EP1 receptor which helps in the treatment of the claimed diseases. However, the specification fails to provide guidance as to whether the diseases listed as EP1-mediated diseases, require the antagonizing of EP1.

The presence or absence of working examples

The only working examples pertains to functional calcium mobilization assays on page 165-166.

There are no other working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease and have no data on the possible treatment of EP1-mediated diseases that require the antagonizing of EP1. Also, the specification fails to provide working examples as to how the listed diseases can be treated by the antagonizing of EP1, i.e. again, there is no correlation between the diseases listed and antagonizing of EP1.

The breadth of the claims

The breadth of the claims is that the compound of the claims can treat any condition which is mediated by the action of PGE2 at EP1, without regards as to the affect of PGE2 or EP1 on the stated diseases.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the antagonizing of EP1 and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the antagonizing of EP1.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claims for the treatment of all conditions, mediated by PGE2 at EP1, as a result, necessitating one of skill to perform an exhaustive search for which PGE2 mediated condition- diseases can be treated by the compounds of the claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which EP1-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 10-12, 17-18, 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "substituted at line 4, page 3 of claim 1, and everywhere else throughout the claims is indefinite and unclear because what these substituents can be are not specified at the claim.

B. In claim 1, line 5, page 3, and everywhere else throughout the claims 2-5, 7, 10-12, 17-18, 20-24 the term "heterocyclyl ring" is unclear. In the specification, the term "heterocyclyl" is defined at lines 19-25, page 13 of the specification, as that it can be "aromatic five or six- membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur". This definition is seems to be redundant of the definition of "heteroaryl" which is also described as a five or six membered aromatic ring.

C. In claim 1, line 13, and everywhere else throughout the claims 2-5, 7, 10-12, 17-19, 20-24 page 4, the term "derivative" is indefinite. What derivatives are the applicant claiming?

Claim 25 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Thomas McKenzie can be reached on 571-272-0670.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
August 18, 2006

THOMAS MCKENZIE, PH.D.
SUPERVISORY PATENT EXAMINER
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